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EXAMINER	
PRASAD, SARADA C	
ART UNIT	PAPER NUMBER
1646	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/269,703	Applicant(s) SAKAMOTO, KENJI	
	Examiner Sarada C Prasad	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *3-5,8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Seq. alignments

Detailed Action

1. Receipt of Applicants' arguments and amendments filed in Paper No. 18 (2/8/02) is acknowledged. Amendment to claim 6 has been entered, and new claims 10-12 have been added. Currently, claims 1-12 are pending, and claims 1-2, 6-7 and 10-12 are under consideration for examination. Claims 3-5, 8-9 are withdrawn from consideration as being non-elected.

The numbering of new claims 8-10, submitted in Paper No. 18 (2/8/02) is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Mis-numbered claims 8-10 have been renumbered 10-12 respectively.

2. The following previous objections/rejections are withdrawn in light of Applicants' amendments filed in Paper No. 18 (2/8/02).

(i) Rejection of claims 6-7 under 35 USC 102(b) as being anticipated by WO9310149.

3. Applicant's arguments filed in Paper No. 18 (2/8/02), have been fully considered but were deemed to be not persuasive. The issues remaining and new issues, are stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

4a. The substitute specification filed in Paper No. 10 (1/19/01) under 37 CFR 1.125 has not been entered, because it does not conform to 37 CFR 1.125(a) or 37 CFR 1.125(b). In the instant case, the marked-up copy showing the amendments to be made via the substitute specification

relative to the specification at the time the substitute specification is filed has not been submitted in full.

4b. The amendment filed in Paper No. 10 (1/19/01) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Substantial changes have been noted in the substitute specification, and are considered new matter (amendment B, deletion of lines 5-12 on page 2, and insertion of a new paragraph after line 4). Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds of Rejection:

Claim Rejections - 35 USC § 112 Second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claim 1 is indefinite in recitation of 'physiologically active peptides' because one of skill in the art would not know definitively as to what are 'included or not included' in the list of physiologically active peptides, or which 'physiological activity' is implied in the claim language, because it is not clear what properties constitute "physiological activities" and what do not so that the metes and bounds of the claims may be determined.

5b. Claim 1 is vague and indefinite in recitation of 'wherein there is a substance or cell present in vivo having a functional antagonism against the ligand or the receptor or against a cell which expresses the receptor of the ligand' because it is not clear to one of skill in the art as to what is meant by 'functional antagonism' and the reference is to which 'substance' or which 'cell' or which 'receptor' or which 'ligand'. The intention of the limitation cannot be determined, and applicant is requested to clarify what is intended by this phrase.

Claim 2 is rejected insofar as it depends on claim 1.

Claim Rejections - 35 USC § 112 first paragraph

6. Claims 1-2 remain rejected under 35 USC § 112 first paragraph for reasons of record set forth in Paper No. 17 (8/10/01) as well as additional reasons provided as follows.

As pointed out in the above 35 USC 112-second paragraph rejection (paragraphs 5a-5b) of claims 1-2, it is not clear what 'physiologically active peptides' are and what is meant by the clause 'wherein there is a substance or cell present in vivo having a functional antagonism against the ligand or the receptor or against a cell which expresses the receptor of the ligand' and the phrase 'functional antagonism', however, given the teachings of the specification it is presumed the missing domain peptides are intended to have an activity affecting the pathway of the receptor from which they are derived, as exemplified by calcitonin receptor.

Response to applicants' arguments:

Applicant asserts that the entire specification provides a sound scientific basis and description for the claimed subject matter. Neither the claims, not the specification are construction blue prints. They are addressed to one of skill in the art. To support a rejection for a non-enablement under 35 USC 112 first paragraph, in view of the well structured specification

and its presumptive enablement, the office must cite references which show inter alia that the specific model utilized here does not translate into other models. Conclusions not supported by references do not create a prima facie case of non enablement which forces the applicant to go forward with rebuttal evidence. Applicant supports his argument in favor of an enabling disclosure for identification of missing domains in any and all transmembrane receptor splice variants and the testing of the functionality as it related to the receptor (Paper No. 18, 2/8/02).

However, this argument is not found to be persuasive, because the specification merely pointed out possible biochemical pathways wherein the missing domains might exert possible physiological activities of the splice variants of the glucagon receptors, and somatostatin receptors. This limited guidance would not be sufficient for one of skill to determine the undescribed physiological activities of the missing domains of 'any and all' variant 7-transmembrane proteins by the instant methods. In fact, the applicant, at the time of filing, was not in possession of the nature of the physiological activities of the instant SEQ ID No. 2 and SEQ ID NO. 3. This situation is analogous to where the applicant is asking for permission to do further experimentation.

What specification sets forth:

Specification sets forth a method of comparing the amino acid sequences or the sizes of the transmembrane receptors to find receptors which have one or more variants in size but are the products of the same gene (page 4, entire 2nd para). After identifying such receptors having one or more variants in size and products of the same gene, the domain in the larger receptor is identified as the missing domain in the smaller receptor (page 4, entire 3rd para). Instant disclosure also points out one such peptide representing the missing domain of a smaller variant

of the calcitonin receptor that binds to receptors present on osteoblasts thereby promoting osteogenesis (paragraphs bridging page 4-5).

Reasons for the rejection under 35 USC 112-first paragraph:

It is possible for one of skill in the art to follow state of the art methods, and isolate missing domains from various receptors of different sizes and synthesize them recombinantly. However, it is not predictable to find 'an associated function' of the missing domain based on a distinct, specific example such as that of the missing domain of the calcitonin receptor as in instant case. For example, identification of missing domains disclosed in the specification for glucagon receptor and somatostatin receptor is not followed by assignment of a particular "physiological activity" associated with the missing domain (Examples 4 and 6).

Therefore, the instant specification is non-enabling for one of skill in the art to predictably assign function to the missing domain and establish that such activity or assigned function is true, because one needs to assign a hypothetical function, and then screen for such. Instant disclosure proposes (page 4 of the specification, 1st para, best mode for carrying out the invention, lines 4-end), hypothetical 'functional antagonisms' such as insulin antagonism for glucagon receptor, or somatostatin antagonism with growth hormones. It is not sufficient for one of skill in the art to predictably assign functional antagonisms for any missing domains of any receptor variants with success based on one example that shows that missing domain has an (un)expected activity. In fact, instant disclosure provided a clue of how to assign function for the missing domains of insulin and glucagon, however, failed to provide any methods that would assist one of skill to realize the expected activities of the missing domains of these two transmembrane receptors. With the current state of the art knowledge, and guidance provided, it

is not feasible for a skilled artisan to plan and practice the invention as claimed because to test and screen 'undescribed activity' in missing domains of which 'transmembrane receptors' in what 'species' and under 'what circumstances'. It is not predictable there would be a pattern or reasonable expectation of success in predicting that any missing domain localized would have certain physiological activity.

Furthermore, Reisine et al. teach variants of somatostatin receptors (page 1017) showing the variant, SSTR3, that exhibits the instant SEQ ID No.3 as part of the difference in the sequence. Teachings of Reisine et al. also point out that the ligand specificities, the regulation by agonist pretreatment of the variants SSR2A and SSR2B are similar, except that SSRT2B is coupled to adenylate cyclase in cos-7 cells, and mediated SRIF inhibition of cAMP formation. The two splice variants namely SSRT2B and 2A differ only in sequence in a limited region at their carboxyl terminus implicating this region of SSR2B in coupling to adenylate cyclase (paragraphs bridging pages 1016-1017). However, this difference in activity is not attributed to the sequence variation in variant SSTR3, which possesses then instant SEQ ID NO. 3 as being part of a larger receptor. Thus, it is evident to one of skill in the art that finding a difference in sequence of the variant receptors is predictable, however it is likely that variant sequences are generated due to variation in sequence spread at various portions of the transmembrane receptors, certain of the variant differences in sequence might be of no consequence, and certain other differences might exert physiological differences in the function/activity of the variant receptors. Therefore, predicting and attributing a physiological activity to the missing domains of 'any and all' of the transmembrane receptors, and realizing it is not predictable.

It is concluded that, the specification, in light of the prior art, is enabling only for generation of the missing domains and has failed to disclose any functional antagonism of the missing domains to those hypothesized in the disclosure (page 4, entire 1st para). The applicants have failed to show any "physiological activity" of the missing domain other than pointing out a possible functional antagonisms.

It is believed that all of applicant's arguments have been addressed and based on the above discussion, predictability in the art, lack of sufficient guidance the 35 USC 112-first paragraph rejection of record is being maintained.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7a. Claims 1-2, 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gorn et al. 1992.

Gorn et al. teaches that the amino acid sequence of the human ovarian calcitonin receptor (hCTR) is 73% identical to pCTR and the hCTR, and identifies an insert of 16 amino acids (instant SEQ ID No. 1) between the transmembrane domains 1 and 2 (abstract, lines 17-20). Once the amino acid sequence of a polypeptide is known, it is anticipated whether is it is made by recombinant methods, or synthetic methods, because the properties of the recombinant as well as synthetic peptide are same. These teachings anticipate the instant identification of a missing

domain of a calcitonin receptor, and therefore anticipate claims 1-2, and 10-12. (see sequence A for the 16 amino acid missing domain).

7b. Claim 1-2, 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Reisine et al. (1994).

Reisine et al. teach variants of somatostatin receptors SSTR2, SSTR2A and SSTR2B, and identify the 12 amino acid difference in the variant SSTR3 (see sequence comparison B) (page 1017) representing instant SEQ ID No. 3. Further, once the amino acid sequence of a polypeptide is known, it anticipated whether it is made by recombinant methods, or synthetic methods, because the properties of the recombinant as well as synthetic peptide are same. Therefore, Reisine et al. anticipate claims 1-2, 6-7.

7c. Claims 1-2, 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9310149 (1993).

WO 9310149 identifies a peptide of 16 amino acid residues 100% identical to the instant SEQ ID No. 1, which represents the missing domain of instant SEQ ID No. 1. Once the amino acid sequence of a polypeptide of SEQ ID No. 1 is known, it is anticipated whether is it is made by recombinant methods or synthetic methods because the properties of the recombinant as well as synthetic peptide are same. Thus, teachings of WO 9310149 anticipate claims 1-2, and 10-11 (see sequence comparison C).

7d. Claims 1-2, and 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9313130 (July 1993).

WO 9313130 identifies a difference in sequence of 12 amino acids, 100% identical to the instant SEQ ID No. 3, in somatostatin receptor variants (see sequence comparison D). Further,

once the amino acid sequence of a polypeptide is known, it is anticipated whether is it is made by recombinant methods, or synthetic methods, because the properties of the recombinant as well as synthetic peptide are same. Therefore, WO 9313130 anticipates instant claims 1-2, and 6-7.

7e. Claims 1-2, and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Nussenzveig et al. (1994).

Nussenzveig et al. identify a 16-amino acid insertion into first intracellular loop (Il) of human CTR that is not present in porcine CTR, rat CTR, or other human CTR (abstract, lines 3-5, and Figure 3. page 28126) which is 100% identical to instant SEQ ID No. 1. Teachings of Nussenzveig et al. also include identification of an association of a 'physiological activity' with the 16-amino acid insertion (see attached figure). Specifically, chimeras containing the Il-loop of human CTR-1 with its 16-amino acid insertion were incapable of stimulating Inositol phosphate formation and the corresponding signal transduction pathway while allowing stimulation of the cAMP pathway (abstract, last 8 lines). Therefore, Nussenzveig et al. anticipates instant claims 1-2, and 10-11.

7f. Claims 1-2, and 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Maget et al. (1994)

Maget et al. teach alternative splicing responsible for the polymorphism of the glucagon receptor mRNAs (Figure 3, page 274), including putative receptor variants that lead to translated products which exhibit a difference of (a) 27 amino acids after lys 91, and (b) 7 amino acids between amino acids 22-28. The 27 amino acid difference represents instant SEQ ID No. 2 (page 273, column 1, 2nd para, lines 5-6,). Thus, teachings of Maget et al. anticipate identification of missing domains in transmembrane receptors as in instant claims 1-2 and 6-7.

7g. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyerhof et al. (1992).

Meyerhof et al. (1992) teach two different variants of rat somatostatin receptors rSSR-28, rSSR-14 that specifically bind to somatostatin-14 (14 amino acid residue long) and somatostatin-28 (28 amino acid residue long). A comparison of the sequences of hSSTR2 (Figure 1, page 10268) with rSSR-28, rSSR-14 shows that they differ in their carboxy terminal end, with rSSR-28 being longest. Figure 1 of Meyerhof et al. (page 10268, see attached figure) also shows the missing domains at the C-terminal end in each of these receptor variants, thus anticipating instant claims 1-2.

7h. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Yasuda et al. (1992).

Yasuda et al. also teach variants of mouse somatostatin receptors (Figure 2, page 20425, see attached figure) with the missing domain of SSTR1 and SSTR2 being present in SSTR3 which also corresponds to instant SEQ ID No. 3, thus anticipating instant claims 1-2, and 6-7.

7i. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Gremlich et al. (1995)

Gremlich et al. teach identification of two different forms of human pancreatic islet GIP (glucose-dependent insulinotropic polypeptide) receptor, each of them differing by a 27-amino acid insertion in the COOH-terminal cytoplasmic tail (Figure 2, page 1204). Thus, identification of the difference in these GIP receptor variants (page 10268) represents identification of a missing domain, and thus anticipates instant claims 1-2.

7j. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Song et al. (1993).

Song et al. identify a pentapeptide 'Gly-Gly-Ala-Gly-Pro', located in the putative third intracellular loop, as being the difference between the two alternatively spliced human Gastrin /CCKB receptor variants, one containing 452 amino acids, and the other containing 447 amino acids (abstract, lines 12-end). Therefore, such identification of a pentapeptide-missing domain by Song et al. anticipates identification of a missing domain in a transmembrane receptor variants as in instant claims 1-2.

7k. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ito et al. (1993).

Ito et al. teach identification of a missing domain of a pentapeptide in the two alternately spliced variant forms of gastrin receptor, thus anticipating instant claims 1-2.

Conclusion

8. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
April 22nd, 2002

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